Failure of "effective" treatment for heart failure to improve normal customary activity

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Abstract

***Objectives*—To examine the effects of drug treatment on laboratory exercise tests in relation to measures of daily activity in patients with chronic heart failure.**

***Setting*—University teaching hospital.**

***Subjects*—18 patients with mild to moderate chronic heart failure (New York Heart Association functional class II-III) and 10 age matched healthy controls.**

***Methods*—Assessments were made before and after 12 weeks of vasodilator drug treatment. Exercise capacity was measured during two different types of treadmill exercise, one using a ramp protocol and the other a fixed work load. Corridor walk tests at three self selected speeds were also undertaken and measures of customary activity assessed from pedometer scores.**

***Results*—Exercise times were significantly increased from baseline ($P < 0.01$) with both treadmill protocols after 12 weeks of drug treatment, with a positive correlation between the duration of treadmill exercise for both protocols ($r = 0.69$, $P < 0.01$). Corridor walk tests of 100 m at a self selected slow speed also improved ($P < 0.02$) but these did not correlate with the changes in treadmill exercise time. The pedometer scores of the patients with heart failure were greatly reduced compared with those of the controls (258 (45) $\times 10^2$ *v* 619 (67) $\times 10^2$ steps/week, $P < 0.001$) and after 12 weeks of treatment were unchanged (261 (42) $\times 10^2$ steps/week).**

***Conclusions*—These data confirm the need to use different exercise protocols when assessing the benefits of drug treatment in patients with chronic heart failure. Treatments that seem effective with conventional laboratory based exercise tests may not improve daily activities. This may reflect a failure of apparently successful treatment and should be considered when intepreting clinical trials.**

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Keywords: chronic heart failure; exercise protocols; exercise capacity; effects of drug treatment

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An improvement in symptomatic wellbeing is an important aim in the treatment of patients with chronic heart failure but the best way of assessing it is not clear. Formerly, favourable changes in central haemodynamic variables were believed to indicate a beneficial effect of treatment but it is now recognised that they may not be matched by changes in the patient's exercise capability.[1 2] As exercise capability is thought to be closely related to wellbeing, laboratory based, symptom limited exercise tests performed on a treadmill or bicycle are the usual way of assessing the effects of drugs. These tests have the advantage of close control but clearly are not representative of the type of exercise that patients perform during normal daily life.[3] Different exercise protocols also seem to give different measures of incapacity and which is the most appropriate is not known.[4]

For these reasons other tests, such as corridor walk tests, in which patients decide their own work load are being used more frequently. These are of two types: those that are also symptom limited, patients walking as far as possible in an allotted time,[5] and those that measure perception of speed in which patients are asked to walk a fixed distance at self selected speeds.[6] Although these tests are more likely to be representative of daily incapacity, they remain laboratory based and as such may still not accurately reflect actual exercise capability outside of this environment.

Assessment of patients outside the laboratory often involves the use of quality of life questionnaires, many of which specifically enquire about levels of daily activity. Additional information may also be obtained using body borne pedometers, which have shown a greatly reduced level of daily activity in patients with heart failure compared with that in normal controls.[4 7] Ideally, an effective drug should be able to increase this aspect of a patient's exercise capability and produce a real improvement in wellbeing. We have analysed results from patients enrolled in ongoing clinical trials to investigate whether an increase in exercise tolerance in laboratory based tests is paralleled by an improvement in daily customary activities.

Patients and methods

PATIENTS

Eighteen patients with moderate to severe heart failure were studied. They were participating in two trials that compared the effects of captopril and the oral dopamine agonist ibopamine, and isosorbide mononitrate and the angiotensin converting enzyme inhibitor,

trandolapril. The patients' ages ranged from 56 to 75 years and 14 were men. The cause of heart failure was ischaemic heart disease in 10 patients, mitral or aortic regurgitation with impaired left ventricular function in four, and dilated cardiomyopathy in the remaining four. All patients were limited on exertion by symptoms of heart failure despite at least 80 mg of frusemide daily (mean (range) dose was 90 (80–160) mg). The studies were approved by the local ethics committee and all patients gave informed written consent.

Customary activity of 10 fit healthy controls of the same age as the patients was measured over a one week period.

METHODS

All patients were evaluated in an identical way. In addition to their normal medication they were given, single blind, placebo treatment. This was continued until their treadmill exercise time measured at weekly intervals using a modified Bruce protocol had reached a plateau and did not increase by more than 5% on two consecutive visits. Patients were then randomised to one of the active treatments and repeat measurements of exercise capacity were made at the end of 12 weeks of treatment.

TREADMILL EXERCISE TESTS

At each visit the patients were asked to exercise to a symptom limited maximum using two different treadmill protocols. The first was a modified Bruce protocol; the speed and slope of the treadmill increasing after three min at each of the following stages:

Stage	I	II	III	IV	V	VI
Speed (km/h)	2·7	2·7	2·7	2·7	4·0	5·4
Slope°	0	1·3	2·6	4·3	5·4	6·3

After at least 45 min of rest the patients were asked to complete a second symptom limited test. The speed and slope of the treadmill were fixed at the equivalent to stage IV of the modified Bruce protocol and patients continued at this work load until stopped by symptoms of heart failure.

Absolute work completed was calculated in kilojoules from standard formulae during both exercise tests.

CORRIDOR WALK TESTS

The patients rested for a further 30 mins after the second treadmill exercise test, and were then asked to walk a 100 m along a corridor at self selected slow, normal, and fast speeds. The time to complete the 100 m walk at these speeds was recorded.

CUSTOMARY ACTIVITY (PEDOMETER SCORES)

At all times during the study the patients wore body borne pedometers to evaluate their physical activity during normal daily activities measured by the total number of steps walked. The methods and pedometers have been validated previously.[8] The scores were recorded at weekly intervals and the pedometers were calibrated at each visit. Pedometers were worn on belts, one at each hip. Scores were accepted only if the readings from both pedometers were within 20% of each other and a mean score was then calculated.

STATISTICAL ANALYSIS

Data are expressed as means (SEM). Analysis of the differences between variables before and after treatment was made with the Wilcoxon signed rank test. Analysis of the relations between the changes of the different variables was performed with Spearman's rank correlation coefficient.

Results

TREADMILL EXERCISE TESTS

The mean (SEM) symptom limited exercise time increased with both treadmill protocols (fig 1). Using the modified Bruce protocol exercise duration increased from 414 (70) s to 651 (68) s ($P < 0·01$). The baseline exercise duration was shorter with the fixed protocol ($P < 0·01$) but this also increased with treatment from 267 (50) s to 541 (106) s ($P < 0·01$). Figure 2 shows the correlation of the changes between the two treadmill protocols after treatment ($r = 0·69$, $P < 0·05$).

The mean (SEM) work performed also increased from 5·81 (1·75) kJ to 13·98 (2·93) kJ ($P < 0·01$) using the modified Bruce protocol, and from 11·88 (2·43) kJ to 34·09 (10·9) kJ ($P < 0·01$) with the fixed protocol. The baseline exercise capability assessed by total work was greater with the fixed protocol than the Bruce protocol ($P < 0·01$). There was a significant correlation between the protocols in respect of work completed ($r = 0·5$, $P < 0·05$).

CORRIDOR WALK TESTS

The mean (SEM) time taken for patients with heart failure to walk 100 m at a self paced slow speed decreased from 109 (6) s to 102 (6) s ($P < 0·02$) after treatment. Treatment had no significant effect at the normal (from 87 (4) s to 85 (5) s) and fast speeds (from 74 (0·2) s to 73 (4) s). There were no significant correlations between the corridor walk tests and any aspect of treadmill exercise tolerance (table).

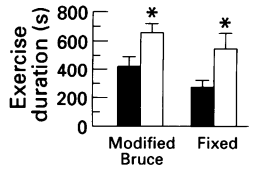

*Figure 1 Effects of drug treatment on treadmill exercise duration. Values are mean (SEM). ■, Before treatment; □, after treatment. * $P < 0·01$, Wilcoxon signed rank test.*

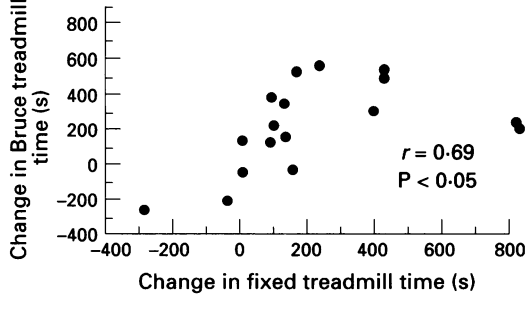

Figure 2 Pairwise correlation of changes in treadmill exercise capacity.

Pairwise correlation of the change from baseline between different exercise tests

	No of patients	*Correlation coefficient*	*P value*
Treatmill time (Bruce)			
v fixed treadmill time	18	0·69	0·02
v slow walk	18	−0·17	0·25
v normal walk	18	−0·08	0·37
v fast walk	18	−0·36	0·07
v pedometer score	18	−0·16	0·26
Treadmill time (fixed)			
v slow walk	18	−0·8	0·13
v normal walk	18	−0·35	0·08
v fast walk	18	−0·26	0·15
v pedometer score	18	0·21	0·21
Walk test v *pedometer score*			
Slow	18	0·14	0·28
Normal	18	0·08	0·37
Fast	18	0·29	0·12

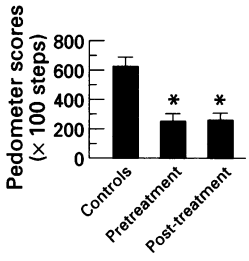

Figure 3 Pedometer scores of patients with heart failure before and after treatment. Values are means (SEM).
** P < 0·001 v controls, Wilcoxon signed rank test.*

CUSTOMARY ACTIVITY (PEDOMETER SCORES)

The mean (SEM) pedometer score for normal controls was 619 (67) × 10^2 steps. The mean (SEM) pedometer score for patients with heart failure was 258 (45) × 10^2 steps over a one week period before treatment ($P < 0·001$). There was no change after 12 weeks of vasodilators, the mean score being 261 (42) × 10^2 steps (fig 3). There was no correlation between the changes in pedometer scores and any other aspect of exercise tolerance either on the treadmill or during the self paced corridor walk tests (table).

Discussion

Although improvement in the quality of life is a major aim of treatment of patients with chronic heart failure, this is not always addressed in clinical trials. Quality of life questionnaires are increasingly used to provide a subjective assessment of symptomatic impairment and response to treatment yet objective measures of exercise capability are frequently used to quantify this, usually in the laboratory on a bicycle or treadmill. Such tests allow close supervision but because protocols have fixed changes in work load the exercise performed is not normal and exercising to a symptom limited maximum is an unusual type of exercise. Furthermore, the most appropriate of the many available protocols is not known.[3,4] For these reasons different measures of exercise capability that relate more closely to a patient's incapacity during normal daily activities would be advantageous. Corridor walk tests are self paced and therefore likely to be a better indicator of incapacity but as they are also conducted under supervision in an institution they may have some of the drawbacks of treadmill tests. A measure of incapacity obtained during normal daily activity should be the best indicator of symptomatic impairment but how it relates to other methods for assessing exercise tolerance is unknown.

In this study patients seemed to have different levels of exercise tolerance when measured on a treadmill with different protocols and depending on the way in which the results were expressed. If exercise time is used as the measure of capability then patients seemed less incapacitated with the Bruce protocol than the fixed work load protocol, while if the results are expressed as total work performed they are more incapacitated with the Bruce protocol. There was no relation between either exercise test and any other of the methods that we used to measure exercise capability so the different tests are measuring different aspects of patient's incapacity. We have also shown that patients had a pronounced reduction in customary activity measured with the pedometers compared with that of the healthy controls.

All patients received active treatment and after 12 weeks' treatment exercise tolerance was improved when assessed on the treadmill. It seems likely that such a significant increase reflects a true response to active treatment rather than a placebo effect, although a placebo control group was not included in the study. There was also a correlation between the changes with both protocols but the magnitude of the changes differed according to the protocol used. This clearly indicates that the measurement of incapacity and the response to treatment are dependent on the exercise protocol used. The treatments also improved the corridor walk test at the self selected slow pace with no significant effect at normal or fast speeds. This is similar to other studies that have reported improvement only at the slow speed.[4,6] There was no correlation between the changes in corridor walk tests and the other tests.

Despite the clear improvement in the laboratory based tests surprisingly there was no change in customary activity measured with the pedometers after treatment. At baseline the patients had a profound reduction in customary activity compared with that of the controls and there was considerable room for improvement. The reason for the lack of improvement is not obvious. Patients may have already adapted their lifestyle to their reduced exercise ability and despite symptomatic improvement did not wish to increase daily activities. Alternatively, the pedometers measure only total steps and do not provide information about speed of walking or rest periods and it may thus be possible that while patients did not increase their total activity they exercised in more comfort with fewer rests.

The results from this study emphasise the need to use different exercise protocols to measure the response of patients with chronic heart failure to treatment. Although symptom limited exercise tests are useful in determining prognosis, tests most representative of a patient's normal daily activities should be used to assess the efficacy of drugs. It is not possible to conclude whether the lack of change in daily activity truly reflects a failed therapeutic response and quality of life assessments may have proved useful in this regard. Measures of customary activity in patients with chronic heart failure has, however,

revealed a failure of apparently "effective" treatment in patients with a laboratory treatment response.

1 Franciosca JA, Goldsmith SR, Cohn JN. Contrasting immediate and long term effects of isosorbide dinitrate on exercise capacity in congestive heart failure. *Am J Med* 1980;**69**:559–66.

2 Massie BM, Krammer BL, Topic N. Lack of correlation between short term haemodynamic effects of captopril and subsequent clinical responses. *Circulation* 1984;**69**: 1135–41.

3 Francis GS, Rector TS. Maximal exercise tolerance as a therapeutic end point in heart failure—are we relying on the right measure? *Am J Cardiol* 1994;**73**:304–6.

4 Cowley AJ, Fulwood L, Stainer K, Hampton JR. Exercise tolerance in patients with heart failure—how should it be measured? *Eur Heart J* 1991;**12**:50–4.

5 Lipkin DP, Scriven AJ, Crake T, Poole-Wilson PA. Six minute walk test for assessing exercise capacity in patients with chronic heart failure. *BMJ* 1986;**292**: 635–7.

6 Cowley AJ, Stainer K, Wynne RD, Rowley JM, Hampton JR. Symptomatic assessment of patients with heart failure: double blind comparison of increasing doses of diuretics and captopril in moderate heart failure. *Lancet* 1986;**ii**:770–2.

7 Hoodless DJ, Stainer K, Savic N, Batin P, Hawkins M, Cowley AJ. Reduced customary activity in chronic heart failure: assessment with a new shoe mounted pedometer. *Int J Cardiol* 1994;**43**:39–42.

8 Bassey EJ, Dallosso HM, Fentem PH, Irving JM, Patrick JM. Validation of a simple mechanical accelerometer (pedometer) for the estimation of walking activity. *Eur J Appl Physiol* 1987;**56**:323–30.